that there must be a different method of regulation. Now Orr-Weaver and colleagues have found a protein complex that might be involved in this regulation.

Underlying the defects

They began by looking at *Drosophila melanogaster* mutants that show a defective rapid embryonic cell cycle, and identified the genes that underlie the defects. These genes encode a protein complex containing a kinase and two activating subunits.

Importantly, the complex specifically regulates the level of mitotic cyclins, says Orr-Weaver, who presented her findings at the International Congress of Genetics in Melbourne, Australia at the beginning of July 2003 (http://www.geneticscongress2003.com/index.php). This is not a localization phenomenon, she adds, the protein kinase complex is controlling the amount of cyclin by regulating either translation or protein degradation.

The findings are unexpected, says Todd Stukenberg, Assistant Professor of Biochemistry and Molecular Genetics at the University of Virginia (http://www.virginia.edu). 'It is quite surprising that this [protein complex] is a regulator of cyclins,' said Stukenberg, who also studies the early embryonic cell cycle. 'There are paradigms [of how cyclins are regulated] that are models in text books that seemed worked out, so if there is a new player, that is important.'

Functional genomics

The researchers are now using a functional genomics approach to search for substrates of the complex. They have already scanned 42% of the *Drosophila* genome and found six candidates. The next step is to find out how these are involved, to try to work out whether the new complex is involved in translation control or protein degradation, they say.

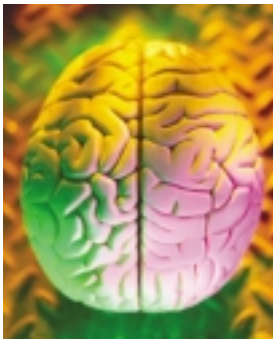
Although mammalian embryos do not have a period of rapid embryogenesis equivalent to that seen in *Drosophila*, understanding the different ways in which cyclins are regulated after transcription will be useful in the study of the normal cell cycle in all organisms, says Orr-Weaver. It might also provide clues to how the cell cycle is coordinated with other developmental events, for instance how it restarts after fertilization, she says.

Stukenberg agrees that understanding the regulation of the modified embryonic cell cycle will be important. The cell cycle has an 'oscillator' signal that regulates the switch from S phase to M phase and back again, he explains. In addition, there are regulatory checkpoints at the entry to each phase. 'You can not study the oscillator in somatic cells because the checkpoints are always a part of it,' he said. 'So, if you want to look at the core oscillator, the early embryonic system is really the only place to look at it. And you can not do that sort of experiment in mammalian cells, because you can not get the cells to be in the same synchronized state.'

News in brief

Targets and Mechanisms

Untangling the AD tangle



The two main molecular events that are characteristic of Alzheimer's disease (AD) brain cells, extracellular amyloid plaques and intracellular neurofibrillary tangles (composed of tau protein), have recently been linked by researchers at the Feinberg School of Medicine, Northwestern University (http://www.feinberg.northwester.edu) [1]. The new findings reveal a novel mechanism involving proteolysing caspases.

Previous investigations, into which of the two pathological entities is the primary cause of AD, already hinted at amyloid promoting assembly of tau into tangles; however, the exact mechanism was not clear. Caspases provided a strong candidate for this 'missing link' as they are known to be activated in degenerating neurons in AD and to occasionally cleave tau.

In experiments exposing neurons to amyloid-β, caspases were activated, which in turn, rapidly (within 2 h) cleaved tau at a conserved aspartate residue (Asp^{421}) in its C terminus. This truncated form of tau (lacking its C-terminal 20 amino acids) was more likely to form tangled filaments than wild-type tau. Indeed, further studies using a specific monoclonal antibody established that the tau protein in the AD tangles was commonly cleaved at the Asp^{421} site. Researchers still have to determine the timing of tau cleavage in AD brains in relation to other events.

This work 'points to the need to consider both of these interrelated pathological events in future studies and therapies' say Lester I. Binder and Vincent L. Cryns, the co-senior authors of the report.

1 Gamblin, C.T. *et al.* (2003) Caspase cleavage of tau: Linking amyloid and neurofibrillary tangles in Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.1630428100 (http://www.pnas.org)

New insight into diabetes

A new system has been designed that could enable the much-needed elucidation of the stages of normal pancreatic

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development and provide a source of insulin-producing cells for the treatment of diabetes [2].

Researchers at the University of Wisconsin-Madison (UW-M; http://www.wisc.edu) evaluated the ability of embryonic stem (ES) cells to differentiate into pancreatic and islet lineage-restricted stages. Cultured in a nonselective medium containing serum, the murine cells differentiated into cells that expressed each of the four major islet hormones, including glucagon and insulin.

During the identification of differentiated cell types, the stages of development were characterized carefully, and, as Jon Odorico – a UW-M Medical School transplant surgeon and senior author of the paper – explains, 'these stages appear to recapitulate many aspects of normal development'. Potentially, the model could be used to identify novel genes and to learn how islets form.

Approximately 17 million people in the USA suffer from diabetes; 5–10% of these are under 20 years of age and suffer from Type I diabetes. In this form of the disease, pancreatic islet cells are destroyed by the immune system and thus, patients must inject themselves with insulin several times a day to regulate blood-sugar levels.

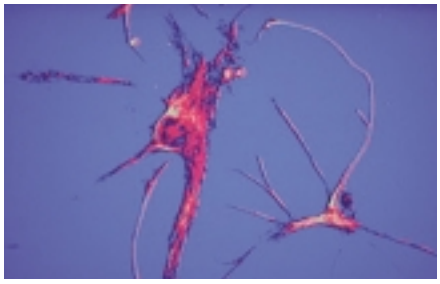
Ideally, these patients need a replacement of islet cells or whole pancreas transplants, but there is a shortage of donors. The ES cells shown in this new model, Odorico suggests, 'could be a source for replacing the patient's own damaged islet cells'. These new findings should lead to better insight into the causes of pancreas-related disorders and the possible development of improved stem cell-based therapies.

2 Kahan, B.W. *et al.* (2003) Pancreatic precursors and differentiated islet cell types from murine embryonic stem cells: an in vitro model to study islet differentiation. *Diabetes* 52, 2016–2024

NO-brainer

The diverse signalling molecule nitric oxide (NO) now has another string to it's bow. It seems that this simple molecule helps to control the proliferation of new neurons in adult mammals [3]. Manipulating this mechanism could be a useful means of combating neurodegenerative disease.

Nearly all neurons in the mammalian brain are produced during embryonic



development. However, at a small number of sites in the CNS, neurogenesis can occur in adults. Such neurons can become fully integrated into the existing brain circuitry. The control mechanisms behind this process are poorly understood, but if a way can be found to trigger neuron proliferation, a therapy to combat neurodegenerative diseases such as Parkinson's and Alzheimer's could be envisaged.

A new clue has been reported by researchers at Cold Spring Harbor Laboratory (http://www.cshl.org/), who studied the role that NO has in the brain. They looked at the expression pattern of neuronal NO synthase, the enzyme responsible for catalyzing NO production, and found that it closely maps to the areas of the adult brain associated with neuron proliferation. They then examined the effects of blocking the enzyme in rats with an inhibitor called L-NAME. Halting NO production led to an increase in neuron proliferation. Furthermore, the neurons appear to contribute directly to the architecture of the rat brain, mirroring the fate of neurons that develop naturally in the adult brain. Further research is now needed to see if these findings can be converted into a therapeutic approach to treating neurodegenerative diseases.

3 Packer, M.A. *et al.* (2003) Nitric oxide negatively regulates mammalian adult neurogenesis. *Proc. Natl. Acad. Sci. U. S. A.* 100, 9566–9571

Supermouse to look at AD plaque formation

A triple-transgenic mouse has been created that will enable the first ever study of both tangle and plaque lesions, the signature lesions of Alzheimer's disease (AD), in a single organism [4]. The mouse hosts three mutant human genes to foster lesion growth: β-amyloid precursor protein, (βAPP; the source of the protein that forms into brain plaques), presenilin-1 (enabling formation of the protein) and tau (the crucial component of tangles).

Researchers at the University of California, Irvine (http://www.uci.edu), have already traced the sequence of molecular events leading to the onset of disease, discovering that β-amyloid plaques appear first in the mouse brain, with tau-laden tangles developing later. Frank LaFerla, co-creator of the mouse together with Salvatore Oddo, explains that this finding 'confirms the human genetic data indicating that plaques are the earliest pathological feature of the disease'.

Alzhemer's disease is the most common cause of dementia, affecting >4 million people in the USA. Most cases are of the sporadic form, which generally affects individuals over the age of 65, with the familial form occurring at a younger age. The mouse study has shown that β-amyloid can accumulate in neural cells before plaques or tangles even form, suggesting that this could be the initiating component of both forms of AD.

The method of creating the transgenic model will produce a uniform genetic background when breeding, thus removing any confounding factors in future analysis. As LaFerla enthuses, this unique mouse model will be useful in the preclinical evaluation of potential Alzheimer's drugs and could 'eventually lead to a single class of drugs for treating both the inherited and sporadic forms of the disease'.

4 Oddo, S. *et al.* (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles. Intracellular abeta and synaptic dysfunction. *Neuron* 39, 409–421

Gene Therapy

Gene therapy for epilepsy

A new treatment for focal epilepsy has been demonstrated in rats [5]. The gene therapy approach offers an entirely fresh platform for treating this dangerous affliction.

Focal seizure in the temporal lobes is one of the commonest forms of epilepsy and is difficult to treat. Removal of abnormal brain tissue is often the only means of preventing further seizures, and this has a poor success rate. A new gene therapy approach from researchers at the University of North

Carolina at Chapel Hill (UNC; http://www.unc.edu/) could form the basis for a less risky alternative treatment.

The team, headed by Thomas McCown, Associate Professor of Psychiatry in UNC's School of Medicine, used an adeno-associated virus (AAV) to deliver the gene for galanin to the cells of the temporal lobes in rats. Galanin is a neuroactive peptide that is known to suppress seizures. Modified AAV was able to deliver the gene efficiently to the cells of the temporal lobes. However, delivery alone was not enough; the gene product is only effective if secreted from the brain cells. To accomplish this, the team also inserted the sequence for fibronectin secretory signal. When activated, this dual construct markedly reduced sensitivity to focal seizures. Furthermore, the antibiotic doxycycline, when ingested by the rats, switched off gene expression, offering a means of controlling the effect.

The technique brings researchers a step closer to affecting only a specific area of the brain. 'In the case of seizures,' explained McCown, 'the area is much more restrictive than that of a single-gene disorder where you need to hit most of the cells in a large proportion of the brain.'

5 Haberman, R.P. *et al.* (2003) Attenuation of seizures and neuronal death by adeno-associated virus vector galanin expression and secretion. *Nat. Med.* 9, 1076–1080

Cancer Targets and Mechanisms

Candidate tumour 'susceptibility' gene identified in humans

A common variant of the gene encoding Aurora2 (*Stk6* in mice, *STK15* in humans) has been identified as a candidate tumour susceptibility gene – one of the first examples of low-penetrance tumour-susceptibility genes in humans [7].

Identification of low-penetrance genes has proved notoriously difficult in the past because they do not segregate as single mendelian traits. To date, many advances in understanding cancer predisposition have involved rare, inherited mutations in high-penetrance genes (e.g. *brca1* and -2 in breast cancer); however, these genes account for less than 10% of cancers. Most cancers result from polymorphisms in numerous low-penetrance genes, and evidence suggests that multiple such genes can confer a dramatic (40–50%) increase in an individual's susceptibility to cancer.

Building on previous work showing that abnormal numbers of copies of the *STK15* are present in more than 50% of colon tumours, Allan Balmain and co-workers at UCSF Comprehensive Cancer Center (University of California, San Francisco; http://cc.ucsf.edu) used linkage analysis and haplotype mapping to identify the culprit as the Phe31→Ile31 variant.

Aurora2 has a key role in maintaining chromosome number during cell division. In the Ile31 mutant, daughter cells inherit extra copies of chromosomes, creating genomic instability, potentially triggering the accumulation of mutations in other key regulatory genes and then cancer.

The next step is to identify inhibitors of the Ile31 variant and establish whether they prevent the recurrence of – or treat existing – colon tumours. Moreover, because the Ile31 variant is thought to have varying activity in other cancers, particularly those that respond to environmental stimuli such as skin and breast, other tumour types should be examined. Finally, the novel technique described by Balmain and colleagues should be used to identify other low-penetrance tumour susceptibility genes, which represent the bulk of the tumour burden.

7 Ewart-Toland, A. *et al.* (2003) Identification of *Stk6/STK15* as a candidate low-penetrance tumor-susceptibility gene in mouse and human. *Nat. Genet.* 34, 403–412

Helping DNA with its packing

In the complex milieu of the cell, DNA has no problem constricting into tight coils for efficient packaging. When researchers handle DNA in solution, however, they often end up with a more extended, voluminous product than they would like. New methods for controlling DNA density *in vitro* might be of considerable use, especially in the field of gene therapy [6].

DNA, in its natural environments, is tightly coiled into structures known as toroids. Trying to mimic this configuration in solution is tricky; the DNA tends to be extended, which causes difficulties when packaging it into vectors for gene therapy, for example. Adding positively charged molecules is the most effective method for condensing DNA, but a consistent and efficient protocol has yet to be devised. However, scientists at Georgia Institute of Technology (http://www.gatech.edu/) have found some ingenious ways of controlling toroidal size.

They introduced specially designed synthetic sequences into a DNA molecule. When the positively charged molecule hexamine cobalt (III) was added, the synthetic region of the DNA bent into two loops. These template loops then induced the remaining DNA to roll into toroidal structures. Serendipitously, a simple means of controlling toroidal size was also borne from this work. The team found that decreasing the salt concentration of the solution below that used in most protocols reduced both the diameter and thickness of the toroids.

Nicholas Hud, Associate Professor of Biochemistry and leader of these studies, explained the importance of his findings. 'By studying the fundamental process of DNA condensation we hope to determine all the factors that help produce particles of smaller size and narrower size distribution,' he said. By combining these factors, he believes, particles optimized for gene therapy could be produced.

6 Conwell, C.C. *et al.* (2003) Controlling the size of nanoscale toroidal DNA condensates with static curvature and ionic strength. *Proc. Natl. Acad. Sci. U. S. A.* 100, 9296–9301

News in Brief was written by *Matt Brown, Lisa Deakin, Clare Rathbone and Georgina Smyth*